

REMARKS

Claims 1-22 are presently pending in the instant Application.

*The Invention is Novel*

Claims 12 and 13 have been rejected under 35 U.S.C. § 102(b) as being anticipated by the teachings of U.S. Patent 4,810,488 (the '488 patent). The Examiner has asserted the '488 patent teaches a crystalline material with a reduced particle size of 2 to 5 microns, wherein the material is an anti-inflammatory steroid. Thus, the Examiner believes the teachings of the '488 patent anticipate Claims 12-13 of the instant Application.

This rejection is respectfully traversed. As the Examiner is aware, the instant Application discloses and claims, *inter alia*, crystalline material containing substantially no amorphous content and having a median particle size of less than 2 microns. Yet, the '488 patent is silent with respect to the amorphous content of the micronized product described therein. In particular, in col. 2, lines 27-36 of the '488 patent, it is explained that a crystalline solvate of an anti-inflammatory steroid, e.g. beclomethasone dipropionate, is produced. Subsequently, the crystalline solvate is dried and micronized to the desired particle size. Moreover, Example 1 in col. 3, lines 9-25 of the '488 patent makes clear that after the crystalline solvate is filtered and vacuumed, it is "...ground to a powder in a pestle and mortar and micronised in a Trost fluid energy mill." Importantly though, it is not taught or implied in the '488 patent that the resulting micronized material possess substantially no amorphous content. MPEP § 706.02 makes clear that "...for anticipation under 35 U.S.C. 102, the reference must teach every aspect of the claimed invention either explicitly or impliedly. Any feature not directly taught must be inherently present." Since there is no teaching in the '488 patent that expressly or impliedly explains that micronized particles described therein contain substantially no amorphous content,

then contrary to the Examiner's assertions, Claims 12-13, as well as Claims dependent thereto are clearly novel with respect to the '488 patent, and should be allowed to issue.

In response to this argument, the Examiner has asserted that the silence of the '488 patent with respect to the amorphous content can be interpreted to mean that no amorphous content is found in/on the crystals. Moreover, the Examiner believes that Applicants have not shown that the '488 patent teaches particles having an amorphous content greater than 5%. Hence, it is the Examiner's position that Applicants arguments are to the contrary and unpersuasive. Thus, the Examiner has concluded that "...no amorphous content is found in/on the crystals."

In response, it is respectfully submitted that, in light of the disclosure of the '488 patent, and knowledge readily available to one of ordinary skill in the art, such an assumption is unreasonable. Hancock, B. & Zografi, G, *Characteristics and significance of the Amorphous State in Pharmaceutical Systems*, J. Pharma. Sciences, 86(1):1-12 (1997), explain that:

The four most common means by which amorphous character is induced in a solid are shown in Figure 1. These are condensation from the vapor state, supercooling of the melt, *mechanical activation of a crystalline mass (e.g. during milling)*, and rapid precipitation from solution (e.g., during freeze-drying or spray drying).

*Id.* At page 1, (emphasis added).

In col. 3, lines 10-16 of the '488 patent, it is explained that in preparing a batch of aerosol units using the solvation technique described therein:

Beclomethasone dipropionate (25 g) was dissolved under heat in isopropyl alcohol (200 ml). The solution was allowed to cool and then placed at 0° C for 24 hours. The resulting crystalline solid was filtered under vacuum and vacuum dried to remove residual solvent. The product was then ground to a powder in a pestle and mortar and micronised in a Trost fluid energy mill.

A similar procedure, also utilizing a Trost fluid energy mill, is set forth in lines 32-38 of the col. 3. *Since '488 teaches the use of a Trost fluid energy mill to micronize the beclomethasone dipropionate, then pursuant to the teachings of Hancock & Zografi, the beclomethasone dipropionate disclosed in the '488 patent must possess an amorphous content.*

Indeed, the '488 patent clearly implies that the beclomethasone dipropionate disclosed therein has an amorphous content. Hancock & Zografi explain that:

As a result of its higher internal energy (*e.g.*,  $\approx 25 \text{ kJ}\cdot\text{mol}^{-1}$  for cephalosporins<sup>3</sup>) the amorphous state should have enhanced thermodynamic properties relative to the crystalline state (*e.g.*, solubility,<sup>4</sup> vapor pressure) and greater molecular motion. We would also expect amorphous systems to exhibit greater chemical reactivity<sup>3</sup> *and to show some tendency to spontaneously crystallize*, possibly at different rates below and above  $T_g$ .<sup>5</sup> From a pharmaceutical perspective we have an interesting situation. The high internal energy and specific volume of the amorphous state relative to the crystalline state can lead to enhanced dissolution and bioavailability,<sup>4</sup> but can create the possibility that during processing or storage the amorphous state may spontaneous convert back to the crystalline state.<sup>5</sup>

(Hancock & Zografi, page 2).

Example 4 of the '488 patent addresses the stability of the beclomethasone dipropionate isopropyl alcohol solvate aerosol formation disclosed therein when stored for six months. In col. 5, lines 10-16 of the '488 patent, it is explained:

After 6 months storage under cycling temperature conditions, *some crystal growth was found* although this was lower than [sic] found in samples of two commercially available suspension aerosol formulations of beclomethasone dipropionate, namely "Becotide" and "Clenil" when subjected to identical conditions (emphasis added).

The passage from Hancock & Zografi, reproduced above makes clear that *amorphous* material may spontaneous revert back to a crystalline. The '488 patent reports some crystal growth occurred during a six month storage of beclomethasone dipropionate micronized using a

Trost fluid energy mill. In light of the teachings of Hancock & Zografi, and the disclosure of the '488 patent, it is truly unreasonable for the Examiner to assume that, because the '488 patent is silent regarding amorphous, one can assume that no amorphous content is found in/on beclomethasone dipropionate disclosed therein. Indeed, the opposite is much more reasonable, i.e. that the beclomethasone dipropionate disclosed therein clearly contains an amorphous content, and that the presence of crystalline material is undesirable.

MPEP § 706.02, clearly states

...for anticipation under 35 U.S.C. 102, the reference must teach every aspect of the claimed invention either explicitly or impliedly. Any feature not directly taught must be inherently present.

Since, in light of the above, the '488 patent teaches the beclomethasone dipropionate disclosed therein has an amorphous content, and since Claim 12 is directed towards, *inter alia*, a crystalline material containing substantially no amorphous content, then the teachings of the '488 patent clearly do not anticipate Claims 12-13, and this rejection should be withdrawn.

#### ***The Invention is Unobvious***

Claims 12 and 13 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over the '488 patent. Although the Examiner has admitted the '488 patent does not specifically teach particles having a median particle size of 1 or 2 microns, the Examiner believes the '488 patent teaches a particle size range to be below 10 microns, and preferably 2 to 5 microns. Moreover, the Examiner believes the active agent is micronized using a fluid energy mill (Col. 3, Examples 1 and 2). It is the Examiner's position that at the time the instant Invention was made, it would have been obvious to one of ordinary skill in the art to vary the particle size of the steroid to achieve a mean particle size of 1 or 2 microns.

Furthermore, Claims 1-22 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over the teachings of U.S. Patent 3,897,010 (the '010 patent) in view of the teachings of U.S. Patent 4,767,612 (the '612 patent) alone, or further in view of the teachings of U.S. Patent 6,145,765 (the '765 patent). The Examiner has asserted the '010 patent teaches a method of milling material wherein the fluid is an inert gas at low temperature (Col. 2, lines 50-65; Col. 4, lines 19-34), and the temperature of the fluid lies in a cryogenic range or a range of the liquification temperatures of the inert gas used in the method (Col. 4, lines 19-34). Moreover, the Examiner has asserted that the purpose of this low temperature is to bring the milling material to a low temperature to embrittle the material to facilitate pulverization of the fluid energy mill (col. 2, line 66 – col. 3, line 17). The Examiner also believes that the temperature of the fluid is reduced to a point such that the material to be milled is no longer plastically or elastically viscous, but ruptures readily upon impact with a surface or another particle (col. 2, line 55 – col. 3, line 17). However, the Examiner has admitted the '010 patent neither expressly teaches the material to be milled is triamcinolone acetonide, nor that the inert gas be helium. The Examiner is of the opinion though that the '010 patent teaches the gas be an inert gas, which encompasses helium.

The Examiner has also asserted that the '612 patent teaches the micronization of triamcinolone acetonide in a fluid energy mill, wherein the particle size range of the micronized triamcinolone acetonide is from 1 to 5 microns (col. 2, lines 55-59). The Examiner has admitted the '612 patent does not teach the complete temperature range. However, the Examiner believes differences in temperature will not support patentability of subject matter encompassed by the prior art unless there is evidence indicate such temperature is critical. In the Examiner's opinion, where general conditions of a claim are disclosed in the prior art, it is not inventive to

discover the optimum or workable ranges by routine experimentation. In support of this opinion, the Examiner has cited *In re Aller*, 22 F.2d 454, 105 USPQ 233, 235 (1955).

In light of the Examiner's assertions described above, the Examiner is of the opinion that at the time the instant Invention was made, it would have been obvious to a person of ordinary skill in the art to mill triamcinolone acetonide in a fluid energy mill at low temperatures to a mean particle size of 2 microns. It is also the Examiner's belief that one of ordinary skill in the art would have been motivated to mill at low temperatures in order to embrittle the milled material to be comminuted, which the Examiner has asserted results in a substantial increase in the throughput of the apparatus for a given energy, and in turn provides a substantial increase of efficiency. Hence, it is the position of the Examiner that the instant Invention as whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the instant Invention was made.

Moreover, the Examiner has asserted that the '765 patent teaches that an inert gas can be used as the fluid for a fluid energy mill, and that the inert gas can be helium. Hence, it is also the Examiner's position that one of ordinary skill in the art would have been motivated to combine the teachings of the '010, '612, and '765 patents, and thus choose a gas that is compatible with the material being processed, and which does not degrade the material upon contact with the fluid, e.g. helium.

In responding to Applicants' previous arguments with respect to these rejections, the Examiner initially pointed out that the prior art is silent as to the amorphous content. The Examiner believes this silence can be interpreted to mean that no amorphous is found in/on the crystals of the art the Examiner cited. Moreover, the Examiner has asserted Applicants have not

shown the prior art, which is silent as to amorphous content, has an amorphous content greater than 5%.

Furthermore, the Examiner has asserted that Applicants have argued that the prior art teaches the temperature range of the gas is in the cryogenic range, which is defined in the prior art. The Examiner believes it is the range of temperatures at which inert gases liquefy but generally teaches below -100° C. Therefore, part of the range overlaps with the instant claimed range of -30° to -120° C. The Examiner also has asserted that Applicants argued that the gas to be used for milling is in liquid form. However, it is the Examiner's position that in the '488 patent, the gas is not in liquid form when used in the energy mill to comminute particles. Thus, it is the Examiner's position that Applicants' argument that the '488 patent teaches away from the instant Invention is unpersuasive.

These rejections are respectfully traversed. With respect to the Examiner's rejection of Claims 12-13 based upon the teachings of the '488 patent, it is respectfully pointed out to the Examiner that MPEP § 2143 clearly states:

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

It is respectfully submitted that none of these criteria have been met in this rejection. As explained above, the '488 patent clearly discloses a material that possesses an amorphous content. Indeed, in light of the passage in col. 5 of the '488 patent reproduced above, wherein it explains that some crystalline growth was observed during a six month storage but less than that

observed after the storage of samples of two commercially available suspension aerosol formulations of beclomethasone dipropionate, one of ordinary skill in the art can conclude that the presence of crystalline material in the formulation disclosed in the '488 patent is undesirable. Furthermore, no teaching or suggestion is present in the '488 patent that would motivate one of ordinary skill in the art to produce a *crystalline* material containing *substantially no amorphous content*, to which Claims 12-13 are directed. Hence, it is unreasonable for the Examiner to assume the material of the '488 patent contains no amorphous character. Thus, Claims 12-13 are clearly unobvious to one of ordinary skill in the art in light of the teachings of the '488 patent.

In addition, Applicants respectfully submit to the Examiner that no motivation or suggestion exists to combine the teachings of the '010 patent with the '612 patent, or to combine the teachings of the '010 patent and the '612 patent with the teachings of the '765 patent. As the Examiner has admitted, the '010 patent teaches the micronization of material. Firstly, the '010, '612 and '765 clearly *mill* material to be micronized. As explained above, Hancock, B. & Zografi clearly teach that *milling* a crystalline material introduces an amorphous character in the materials described in these patents. In stark contrast, the instant invention is directed towards, *inter alia*, a method for A method for producing a fine, *highly crystalline material* product, as well as to a crystalline material containing substantially no amorphous content. Indeed, on page 2, lines 1-15 of the instant Specification, Applicants explain that the instant Invention overcomes the inherent introduction of introducing amorphous character with milling "...by using helium as milling fluid." *No teaching exists in any of these references to combine them as the Examiner has done in order to come up with a method for producing a fine, highly crystalline material.*

Furthermore, as previously explained to the Examiner, the '010 patent teaches the use of

liquefied gas in its milling process. In particular, in col. 4, lines 19-30 of the '010 patent, it is explained:

Still another feature of the present invention resides in the cooling of the driving-gas stream in a plurality of stages, for example including an initial stage in which it is cooled by heat exchange with the expanded cold gas stream to a low temperature and a second stage in which externally supplied cold brings the gas to still lower temperatures, e.g., in the cryogenic ranges ("lowest temperatures"). The term "cryogenic temperature" or "cryogenic range" is intended to refer to temperatures in the range of the *liquefaction temperatures of such gases* such as argon and other inert gases, nitrogen, oxygen, or therebelow.

(Col. 4, lines 19-30 of the '010 patent (emphasis added)).

In stark contrast, Claim 1 of the instant Application is directed towards a method for producing a fine, highly crystalline material product that comprises fluid energy milling a crystalline material using a milling fluid comprising helium, wherein the temperature of the milling fluid is between *-30° C and -120° C*. Since the boiling point of helium is *-268.6° C* (approx. 4 K), *it is impossible for helium used in a method of pending Claim 1 to be in a liquefied form*. Thus, the '010 patent, which requires a *liquefied* fluid, actually *teaches away* from Applicants' Invention.

The Examiner though has asserted the '010 patent teaches the gas is not in liquid form when used in the energy mill described therein, and cites col. 4, lines 19-34; col. 5, lines 5-21; col. 6, lines 42-58; and col. 7, lines 8-28 of the '010 patent for support of this belief. However, it is respectfully submitted the Examiner is incorrect in this belief. In col. 7, lines 12-13 of the '010 patent, it is made clear:

In the heat exchanger 5, the compressed gas is cooled to a *cryogenic temperature* and *enters the jet mill 6* in the usual manner (emphasis added).

It is noted that all of the passages cited by the Examiner refer to a “cold gas stream.

However, this gas stream is not used for milling, but rather for *cooling the material to be milled*.

Col. 4, lines 6-11 of the '010 patent make clear:

*A portion of the cold gas stream may be branched from the mainstream and may be passed through the material to be milled before it enters the milling zone (emphasis added).*

Yet, the fluid that is used in the milling process is indeed in a cryogenic state. Col. 7, lines 8-19 further clarifies this arrangement:

The operation of the system of FIG. 1 will be immediately apparent. The compressed gas, which may be at a pressure of 8 atm g and may be nitrogen, is cooled in the water cooler 4 before entering the heat exchanger 5. In the heat exchanger 5, the compressed gas is cooled to a *cryogenic temperature* and enters the jet mill 6 in the usual manner. A portion of the gas is diverted through column 7 and expands therein to precool the material, which may be polyethylene granules, to a low temperature, the embrittled granules being carried into the mill 6 and therein comminuted to a particle size of the order of microns (emphasis added).

Combining the teachings of the '010' patent with the '765 patent does not overcome the extreme disparity between the instant Invention and the teachings of the '010 patent. In particular, the '765 patent is silent with respect to the temperature at which milling with an inert gas, e.g. helium would be performed, and specifically states that the fluid used in the energy mill described therein is a “gaseous fluid” (col. 2, line 15 of the '765). Thus, contrary to the Examiner's beliefs, no motivation or suggestion is present in either the teachings of the '010 or '765 patents for one of ordinary skill in the art to combine their teachings as the Examiner has done in making this rejection. Indeed, it appears that *Applicants' disclosure* has provided the Examiner with the motivation to combine these references in an unsuccessful attempt to reconstruct Applicants' Invention. Thus, the Examiner has impermissibly utilized hindsight in

an unsuccessful attempt to reconstruct Applicants' Invention from this combination of references. The Examiner cannot rely on hindsight to arrive at a determination of obviousness. *In re Fritch*, 23 U.S.P.Q.2d 1780, 1784 (Fed. Cir. 1992). The Court of Appeals for the Federal Circuit has stated that "selective hindsight is no more applicable to the design of experiments than it is to the combination of prior art teachings. There must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the Applicant's disclosure." [*Interconnect Planning Corporation v. Fed.*, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985)]. *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988).

The Examiner has also asserted that the limitations Applicants relied upon for their previous arguments to overcome this rejection are not recited in the independent claims. Hence, the Examiner fails to see the criticality of such limitations. Yet, the limitation relied upon in distinguishing the instant Invention the combination of references cited by the Examiner, namely that the helium used in the instant Invention is gaseous, is indeed inherently present in Claim 1. In particular, Claim 1 is directed towards a method for producing a fine, highly crystalline material product, the method comprising fluid energy milling a crystalline material using a milling fluid comprising helium, wherein the temperature of the milling fluid is between -30° C and -120° C. As explained above, the boiling point of helium is -268.6°. *Since the instant invention utilizes a milling fluid having a temperature between -30° C and -120° C, and since helium boils at -268.6, then in a method of the present invention as set forth in Claim 1 and Claims dependent thereto, the helium must be gaseous, and not liquefied.*

Finally, in response to the Examiner's citing of *In re Aller*, 22 F.2d 454, 105 USPQ 233, 235 (1955) to support the opinion that where general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine

experimentation, Applicants respectfully submit that *Aller* is not applicable in the instant situation. In *Aller, supra.*, the issue before the Court of Customs and Patent Appeals was whether changes in the temperature at which a chemical process for producing phenol amount to an invention. *Id.* At 234. The prior art stated that the process should be performed at 100° C, while the Claim before the court stated the process should be performed at between 40° C and 80° C. *Id.* In the instant matter, however, the temperature change is substantially greater, and results in the use of a different physical phase, i.e. the instant invention utilizes at temperature at which helium gas, while '010 patent utilizes *cryogenic temperatures*. Furthermore, the court in *Aller, supra.*, explained that "...[u]nder some circumstances, however, changes such as [a change in temperature] may impart patentability to a process if the particular ranges claimed produce a new and unexpected result which is different in kind and not merely in degree with the results of the prior art" *Id.* at 235. In the instant matter, the use of a milling fluid comprising helium at a temperature between -30° C and -120° resulted in a substantially crystalline material product. Such a result is clearly new and unexpected in light of the references cited by the Examiner.

For all of the foregoing reasons, it is respectfully submitted that these rejections be withdrawn, and the Claims be allowed to issue.

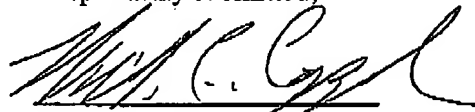
#### *Fees*

No fees are believed to be necessitated by the instant response. However, should this be in error, authorization is hereby given to charge Deposit Account no. 18-1982 for any underpayment, or to credit any overpayments.

**CONCLUSION**

Applicants respectfully request entry of the foregoing amendments and remarks in the file history of the instant Application. The Claims as amended are believed to be in condition for allowance, and reconsideration and withdrawal of all of the outstanding rejections is therefore believed in order. Early and favorable action on the claims is earnestly solicited.

Respectfully submitted,



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